

Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis

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Background: In clinical trials, only about 60% of subjects report an excellent response to intranasal steroids, suggesting a need to add therapies to intranasal steroids to provide additional efficacy.

Objective: To determine whether the combination of fluticasone furoate and oxymetazoline is more efficacious than either agent alone, and to determine whether rhinitis medicamentosa develops after treatment.

Methods: We performed a double-blind, double-dummy, randomized, placebo-controlled parallel study. Sixty patients with perennial allergy were randomized to 4 weeks of once-a-night treatment with fluticasone furoate, oxymetazoline hydrochloride, the combination, or placebo. They were monitored during treatment and for 2 weeks posttreatment.

Results: The total nasal symptom score over the 4 weeks of treatment was lower with the combination (median, 143; range, 30-316) compared with treatment with placebo (262; 116-358) and oxymetazoline alone (219; 78-385; ANOVA, $P = .04$). When acoustic rhinometry was compared between the groups at the end of 4 weeks of treatment, the combination resulted in significantly higher nasal volume (mean + SEM, 15.8 + 1.1 mL; $P < .03$) compared with both placebo (12.1 + 0.9 mL) and oxymetazoline (12.4 + 0.8 mL) alone. The quality of life data showed no significant differences among the groups. Peak flow showed a nonsignificant improvement with the groups on fluticasone furoate. There was no evidence of rhinitis medicamentosa.

Conclusion: The addition of oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. The lack of development of rhinitis medicamentosa suggests the need for a large multicenter study to develop a once-a-day combination of an intranasal steroid and a long-acting topical decongestant. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Allergic rhinitis, perennial, fluticasone furoate, oxymetazoline, clinical trial, rhinitis medicamentosa

Allergic rhinitis is a common condition affecting as many as 40 million people in the United States.¹ The recommended first-line treatment of patients with moderate to severe symptoms of allergic rhinitis is use of an intranasal steroid.¹ Intranasal steroids improve all nasal symptoms and the patients' quality of life. Despite the efficacy of intranasal steroids, only about 60% of subjects achieve excellent relief in clinical trials, suggesting the need for improved treatment modalities. Thus, clinicians have given additional treatments to improve the efficacy of intranasal steroids.²

Although the effects of intranasal steroids can be seen as early as 12 hours after administration, their maximum efficacy takes days. This delay in the onset of action prevents instant recognition of the effectiveness of the intranasal steroid. Shortening the onset of symptom relief with oxymetazoline hydrochloride (OXY) should provide recognizable relief within minutes.

Oxymetazoline is an adrenomimetic that nonselectively agonizes α_1 and α_2 -adrenergic receptors³ and endothelial postsynaptic α_2 receptors, resulting in vasoconstriction in nasal vascular beds when applied locally. Vasoconstriction of vessels results in relief of nasal congestion by increasing the diameter of the airway lumen.⁴ Oxymetazoline has a nearly instantaneous onset of action (5-10 minutes), and its duration of action is estimated to be between 5 and 6 hours. Because of oxymetazoline's duration of action and because nasal congestion can interfere with sleep, we chose to administer it once daily, at night, in this study. Whereas its immediate reduction of nasal congestion is potent, long-term oxymetazoline therapy is hindered by its potential to cause rhinitis medicamentosa, a condition characterized by rebound nasal congestion and histologic nasal mucosal changes.⁵

Whereas clinical observation supports the development of rhinitis medicamentosa as a consequence of overzealous oxymetazoline administration, we question the frequency of this event described in warnings in the *Physicians' Desk Reference*. In actuality, it is likely that once-daily rather than 3 times per day dosing of oxymetazoline is safe. If rebound nasal congestion does indeed occur with once-daily dosing, the simultaneous use of an intranasal steroid might be expected to delay its development.⁶ We hypothesized that the once-daily combination of OXY and fluticasone furoate (FF) would provide superior symptomatic relief for patients with perennial allergic rhinitis compared with FF alone without inducing rhinitis medicamentosa.

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Abbreviations used

FF: Fluticasone furoate
 FF/OXY: Fluticasone furoate/oxymetazoline hydrochloride combination
 NPIF: Nasal peak inspiratory flow
 OXY: Oxymetazoline hydrochloride
 RQLQ: Rhinitis Quality of Life Questionnaire

METHODS**Study design**

We performed a 6-week, 4-group, parallel, randomized, double-blind, double-dummy, clinical trial in 60 patients with perennial allergic rhinitis. After an initial screening with an allergy questionnaire and skin puncture testing to confirm an allergic response to a perennial allergen (cat, dog, dust mite, indoor mold), qualified individuals were randomized into 1 of 4 treatment groups. The 4 groups received the following treatments: placebo, OXY (0.05%, 2 puffs in each nostril every evening), FF nasal spray (110 µg per day), and FF nasal spray plus OXY (FF/OXY). All participants received 2 nasal sprays at night, with 1 spray containing FF or its placebo, the other oxymetazoline or its placebo. The nasal sprays were labeled with participant code numbers, and the investigator assigned participants in a sequential randomized fashion to a study code number in blocks of 4. Dropouts were replaced until 60 subjects were randomized. Replacement subjects were assigned the next sequential treatment. Thus, the number of subjects in each group was not exactly 15.

Eligible participants completed the Rhinitis Quality of Life Questionnaire (RQLQ)⁷ and underwent measurement of nasal volume by acoustic rhinometry before starting the study. Participants were instructed to keep a diary of daily symptoms, nasal peak inspiratory flow (NPIF) meter readings, and medication use during the study; no rescue medications were allowed. The severity of sneezing, rhinorrhea, nasal congestion, and other symptoms was recorded in the morning (reflective of symptoms overnight) and evening (reflective of daytime symptoms) on a 0 to 3 scale. Intake of the study medication was performed once daily, at night, after recording of symptoms and NPIF values. Subjects returned to the nasal laboratory every 2 weeks for a total of 4 weeks for review of the symptom diaries, replacement of medications, performance of acoustic rhinometry, and completion of the RQLQ. After the fourth week, participants stopped treatment, returned medication, and continued with the clinical trial for 2 additional weeks. During this time, they maintained symptom diaries and NPIF measurements twice daily. At the end of the 2-week period, participants returned to the nasal laboratory to perform a final acoustic rhinometry, complete an RQLQ survey, and return the diaries.

Written informed consent was obtained from all participants before enrollment. This study was approved by the Institutional Review Board at the University of Chicago, and the study was registered at <http://clinicaltrials.gov> (#NCT 00584987).

Subjects

Healthy adults between the ages of 18 and 55 years with perennial allergic rhinitis were recruited between November 14, 2007, and May 21, 2009. All patients had a positive skin puncture test to a perennial allergen, symptoms of allergic rhinitis, and a combined nasal morning and evening score ≥ 4 for nasal congestion

on the day preceding entry into the study. Their combined morning and evening total symptom score had to be greater than or equal to 8. The following patients were excluded from this study: patients with a history or physical examination suggestive of renal, hepatic, or cardiovascular disease; pregnant or lactating women; participants treated with systemic or topical corticosteroids during the previous 30 days; participants treated with oral antihistamines or decongestants during the previous 7 days; participants treated with immunotherapy; participants on chronic antiasthma medications; participants with nasal polyps or a significantly deviated septum; and participants with a history of an upper respiratory infection within 14 days of study entry. Ultimately, 64 participants were enrolled, with 4 failing to complete the study, 3 because of noncompliance and 1 because of a sore throat.

Acoustic rhinometry

Acoustic rhinometry, a quantitative measurement of nasal volume, was performed with an ECCOVISION acoustic rhinometer (Hood Laboratories, Pembroke, Mass). Each participant's nasal volume was measured between 0 and 8 cm. Three measurements were made on each side and averaged. The sum of the averages of the right and left was reported.

Nasal peak inspiratory flow

Nasal air flow was measured objectively in liters per minute with an In-Check Peak Inspiratory Flow Meter (Ferraris Medical Inc, Orchard Park, NY). Subjects obtained 3 readings every morning and every evening and recorded the best flow measured. The morning and evening NPIF measurements were summed for the 24-hour period and analyzed.

Statistical analysis

The primary outcome was the symptom of nasal congestion. Other outcomes were symptoms of runny nose and sneezing, other symptoms, total symptom score, RQLQ, and acoustic rhinometry and NPIF measures.

To compare treatments, we used a cumulative symptom score obtained by adding the symptoms obtained on all 28 days of treatment. Because the scores were not normally distributed, we compared the cumulative scores among treatments by Kruskal-Wallis ANOVA followed by Mann-Whitney testing for *post hoc* analysis. NPIF data were not normally distributed and were analyzed like nasal symptom scores. Quality-of-life and acoustic rhinometry data were normally distributed and were analyzed by use of ANOVA with Bonferroni testing for *post hoc* analysis.

To examine the data for a possible rebound effect after cessation of therapy, we performed a Friedman ANOVA on the last day of treatment (day 28) and the 14 days after treatment cessation. If the analysis showed significant differences, we performed a *post hoc* analysis by using the Wilcoxon signed-rank test to compare the last day on therapy to the posttreatment days. Further, to make certain that there were no significant rebound effects, we compared the first day of treatment to the last day after cessation of therapy by using the Wilcoxon signed-rank test.

RESULTS

We screened 83 subjects and entered 64 subjects into the study. Four subjects dropped out, and 60 subjects completed the study.

TABLE I. Baseline characteristics

Parameter/ treatment	FF	OXY	FF/OXY	Placebo
No.	15	16	15	14
Age (y), mean (SEM)	30.5 (2.2)	26.9 (1.3)	28.8 (2.3)	29.1 (3.0)
Sex (M/F)	3/12	7/9	6/9	5/9
Skin test (no. positive)				
Dust mite	15	15	12	13
Cat	0	0	0	0
Dog	0	0	0	0
Mold	4	7	6	5
Dust mite wheal (mm), mean (SEM)	8.4 (0.8)	9.4 (0.7)	11.6 (1.4)	9.7 (1.4)
Baseline symptom score (12-h reflective) (SEM)	6.3 (0.9)	5.0 (0.8)	4.6 (0.7)	6.2 (0.7)
Acoustic rhinometry, mean (SEM)	11.3 (0.6)	12.0 (1.1)	12.5 (0.8)	11.7 (0.7)
RQLQ (overall visit 1), mean (SEM)	3.25 (0.29)	2.99 (0.28)	2.6 (0.22)	3.07 (0.28)
NPIF, median (range)	90 (50-200)	90 (50-150)	90 (50-200)	90 (70-190)

F, Female; M, male.

The groups were matched at entry for age, sex, skin test sensitivity, baseline symptoms, nasal volume, quality of life, and air flow (Table I). Table II lists the adverse events.

Nasal congestion symptoms

When the cumulative congestion scores were examined, treatment with FF and FF/OXY led to greater reduction in the nasal congestion symptom score than did placebo or OXY ($P = .025$). *Post hoc* analysis showed that the reduction compared with placebo approached statistical significance with FF ($P = .06$) and achieved statistical significance with the combination of FF/OXY ($P = .003$; Fig 1; Table III). To assess whether any treatment resulted in faster onset of action, we analyzed the sum of stuffy nose scores for the first 3 days of therapy. There was no significant difference by ANOVA ($P = .17$).

We then compared the symptoms on the last day of active treatment to the posttreatment day scores within each treatment arm and showed that there were no significant changes while the patients were on placebo ($P = .25$) and OXY ($P = .18$), and there was a significant difference with the patients on FF and FF/OXY ($P < .001$). A significant increase in stuffy nose symptoms occurred on almost all postcessation treatment days compared with the last day on active treatment ($P < .04$) with FF and FF/OXY. On both treatments, the last study day was not different from the last day of treatment. To test further for rebound, we compared the first day of active treatment with the last day after cessation for all treatment arms and showed that stuffy nose score was significantly lower after cessation of treatment when patients were on placebo (first day, median [range], 4.0 [2-6]; last day, 1.5 [0-5]; $P = .03$), FF (first day, 4.0 [2-6]; last day, 1.0 [0-6]; $P = .006$), and FF/OXY (first day, 4.0 [0-6]; last day, 1.0 [0-3]; $P = .03$) and was lower, but not significantly so, after OXY (first day, 4.0 [0-5]; last day, 1.0 [0-6]; $P = .7$).

TABLE II. Adverse events

Adverse event	FF/OXY	FF	OXY	Placebo	Total
Headaches	2	4	2	2	10
Migraine	1	0	1	0	2
Cold/virus	2	1	3	1	7
Sore throat	1	0	0	0	1
Menstrual cramps	0	0	1	0	1
Bloody secretions	2	0	0	1	3
Asthma flare-up (prednisone)	0	1	0	0	1
Swine flu	0	0	0	1	1

Total nasal symptoms

When the individual treatment day scores were examined, treatment with FF and FF/OXY led to more reduction in total nasal symptom scores than did placebo or OXY (Fig 2; Table III). Cumulative scores for each group during the 28 days of treatment was significantly different among treatments ($P = .04$; Fig 3; Table III) and was lowest for the combination treatment with FF/OXY compared with placebo ($P = .007$) and OXY alone ($P = .036$). The combination resulted in lower symptoms than in the group on FF alone ($P = .074$).

To examine the early effect of treatments, we calculated the cumulative symptoms for the first 3 days of therapy and analyzed them. There was an overall significant difference among treatments ($P = .04$) with the combination of FF/OXY resulting in lower symptoms than did placebo ($P = .014$) or FF ($P = .02$), but not OXY alone ($P = .1$). Further, FF alone did not result in a significant lowering of nasal symptoms compared with placebo. These data suggest that the addition of OXY to FF results in faster onset of symptom relief than does FF alone. The individual symptoms of runny nose and sneezing showed similar trends. We also found similar results for total symptoms minus the nasal congestion score (Table III).

We then compared the symptoms on the last day of active treatment to the last study day scores within each treatment arm and showed that there were no significant changes while the patients were on placebo ($P = .09$), and a significant difference occurred with the patients on OXY ($P = .05$), FF, and FF/OXY ($P < .001$). A significant increase in total nasal symptoms on almost all postcessation treatment days occurred compared with the last day on active treatment ($P < .04$) with FF and FF/OXY. On OXY, there was a significant increase on only days 1 and 2 postcessation ($P < .05$) and a decrease on the last study day ($P < .05$). To test further for lack of rebound, we compared the first day of active treatment to the last day after cessation for all treatment arms and showed that total nasal symptom scores were not significantly different for placebo, OXY, and FF/OXY. The patients on FF had a significantly lower score after cessation of treatment than on the first day of active therapy ($P = .006$; Fig 2).

Acoustic rhinometry

Acoustic rhinometry was measured at baseline and at the 2-week (middle of treatment) and 4-week (end of treatment) time points and 2 weeks after discontinuation of treatment (week 6). There were no significant differences in acoustic rhinometry values at baseline ($P = .76$; Fig 4). Two weeks after the initiation of treatment, there was an overall significant difference among the

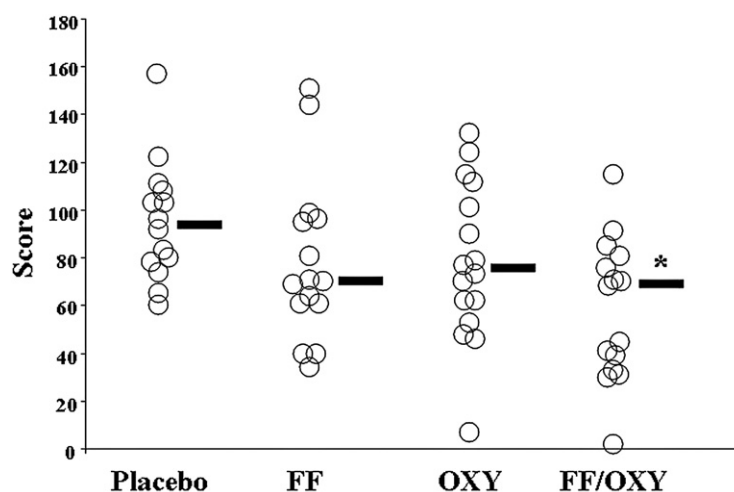


FIG 1. Cumulative nasal congestion score for all 28 days of active therapy. Different treatments are displayed on the x-axis, and individual data are shown with solid bars representing median responses. * $P = .003$ versus placebo.

TABLE III. Nasal symptom scores

Sx	Period	ANOVA	PL	OXY	FF	FF/OXY
Snz	3 d	.11	4 (1-13)	4 (0-13)	6 (0-18)	1 (0-17)
Snz	28 d	.24	37 (2-133)	34 (4-96)	32 (0-103)	19 (0-107)
RN	3 d	.08	9 (1-18)	6 (0-15)	8 (1-14)	5 (0-11)
RN	28 d	.045	72 (18-157)	56 (6-104)	59 (5-115)	29 (6-84)*
SN	3 d	.18	13 (4-18)	11 (3-17)	12 (6-18)	8 (0-17)
SN	28 d	.03	94 (60-157)	75 (7-132)	70 (34-151)	68 (2-115)*
Other	3 d	.63	9 (0-16)	8 (0-15)	7 (0-12)	4 (0-15)
Other	28 d	.4	64 (6-134)	55 (0-102)	31 (0-95)	17 (0-117)
Total	3 d	.04	30 (12-63)	28 (7-60)	33 (9-50)	20 (0-56)*†
Total	28 d	.04	262 (116-358)	219 (78-385)	201 (68-395)	143 (30-316)*
Tot-SN	3 d	.087	22 (5-45)	16 (2-43)	23 (3-37)	11 (0-43)
Tot-SN	28 d	.113	174 (35-420)	142 (16-253)	120 (8-277)	76 (9-234)

3 d, Cumulative score over first 3 days of treatment; 28 d, cumulative score over all 28 days of treatment; Other, itchy nose, throat; PL, placebo; RN, runny nose; SN, stuffy nose; Snz, sneezes; Sx, symptom; Tot-SN, total symptoms excluding stuffy nose symptoms.

Numbers in the ANOVA column represent P values. Numbers in other columns represent median (range). Boldfaced values below ANOVA represent significant values.

* $P < .02$ versus placebo.

† $P = .02$ versus FF.

groups ($P = .003$), with the group on FF/OXY showing a significantly larger nasal volume (less nasal blockage) than did the subjects on placebo ($P = .01$) and OXY ($P = .02$). At 4 weeks after the initiation of treatment, there was an overall significant difference among the groups ($P = .009$), with the group on FF/OXY showing significantly larger nasal volumes than did the subjects on placebo ($P = .014$) and OXY ($P = .025$). Treatment with FF alone did not result in a significant improvement in nasal volume compared with placebo at either the 2-week or 4-week treatment time points. Although the combination therapy was numerically superior to the FF arm in nasal volume measurements, these differences were not statistically significant.

Two weeks after stopping of medication (week 6), the values were not different from the 4-week time point except for a reduction in volume in the FF/OXY group ($P = .04$). When the final visit was compared with baseline, there were no significant differences in nasal volume in the groups on OXY and placebo. The groups on FF and FF/OXY had higher nasal volumes 2 weeks after cessation of treatment compared to baseline ($P < .04$). This

suggests the absence of rebound nasal congestion after cessation of OXY treatment.

Quality of life

The groups showed typical and similar entry scores for the overall domain of the RQLQ ($P = .39$; Table I). The overall domain within each treatment showed a significant improvement in quality of life ($P < .01$; Fig 5). All treatments led to a significant decrease ($P \leq .02$) in the overall domain that was ≥ 5 , suggesting a clinically relevant improvement. There were no significant differences among treatments at any of the measured time points or in any of the subdomains.

NPIF

Daily NPIF values were numerically higher throughout therapy for the groups on FF and FF/OXY, compared with placebo and OXY, indicating more patent nasal airways (Fig 6). There were no

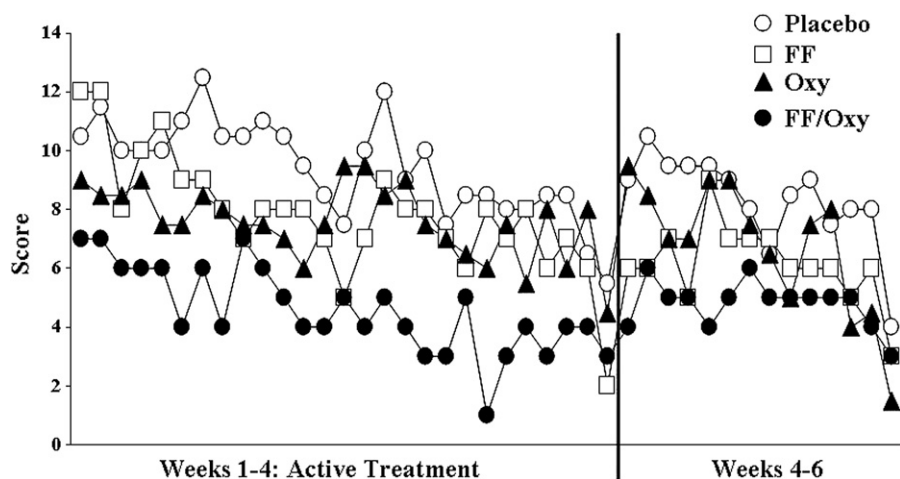


FIG 2. Total nasal symptom score (sum of AM and PM scores) during the 4 weeks of active treatment and the 2 weeks after cessation of therapy. The solid vertical line represents cessation of therapy. Data are displayed as medians.

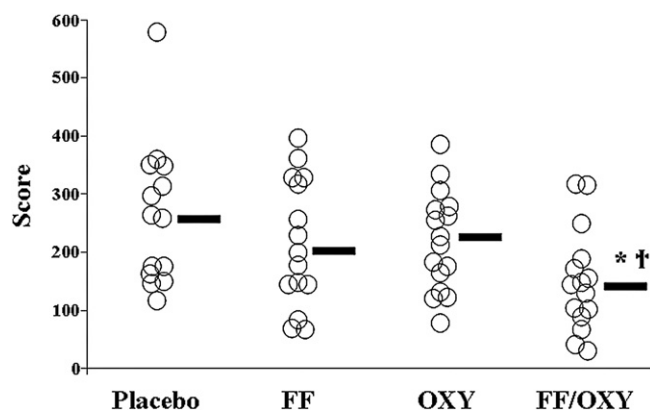


FIG 3. Cumulative total nasal symptom score for all 28 days of active therapy. Different treatments are displayed on the x-axis, and individual data are shown with solid bars representing median responses. * $P = .007$ versus placebo. † $P = .04$ versus OXY.

significant differences in NPIF among treatment groups for the total values and the values obtained in the morning. When the evening values were analyzed, there was a significant difference among groups ($P = .04$). NPIF was higher after treatment with FF ($P = .009$) and FF/OXY ($P = .027$) compared with OXY alone. To test for rebound, we compared the first day of active treatment with the last day after cessation for all treatment arms and showed that total NPIF was not significantly different for placebo, OXY, and FF/OXY. The patients on FF had a significantly higher NPIF after cessation of treatment than on the first day of active therapy ($P = .02$; Fig 6).

DISCUSSION

Even with a relatively small numbers of subjects, we were able to show a numerically superior effect of adding oxymetazoline to FF on most parameters assessed. In some of these analyses, we were also able to show a statistically significant superior effect of the combination compared with FF alone. When nasal congestion was examined for the duration of the 4 weeks of therapy, FF/OXY resulted in a significant improvement compared with placebo,

whereas FF only approached statistical significance. When total nasal symptoms were examined for the 4 weeks of therapy, again we saw a significant improvement from placebo for the combination, but not for FF alone. The combination was statistically superior to OXY alone and was almost statistically superior to FF. When total nasal symptoms for the first 3 days of therapy were analyzed, the combination of FF/OXY provided statistically superior efficacy compared with FF. FF/OXY resulted in a statistically larger nasal volume than did placebo at the 2-week and 4-week time points, whereas FF alone achieved numerical but not statistical improvement. Furthermore, FF/OXY was numerically and statistically superior to OXY alone at both time points. This study was performed with a small number of patients; larger numbers would probably have led to the combination achieving consistent statistical superiority compared with both individual components used alone. Furthermore, the benefit of the combination appeared to be more global than the symptom of congestion, because it was achieved with total nasal symptoms that also included sneezing, runny nose, and nasal itching.

In addition to being an α -agonist, oxymetazoline has been shown to have various antioxidative and anti-inflammatory properties.⁸⁻¹² Whether any of these effects contributed to our results is unknown. The oxymetazoline was dosed once daily at night. The initial thought was that the decongestant would improve airflow, and patients would sleep better. Our symptom scores and peak flow measurements were obtained before dosing and in the morning. These time points were chosen because they occur after the duration of action of oxymetazoline. Thus, only the morning reflective score for congestion would be expected to be affected by this strategy. In reviewing the overall data, we found that there were significant effects on most of the individual symptoms obtained both morning and evening, supporting the additive effects of the oxymetazoline/FF combination beyond its decongestant effect.

A major concern about the regular usage of oxymetazoline is the development of rhinitis medicamentosa. The exact mechanism of the development of this undesirable effect or its frequency of development with prolonged use of oxymetazoline is unknown. The initial development, however, is believed to be linked to the loss of α -receptors.¹³ Patients with a long history of the problem

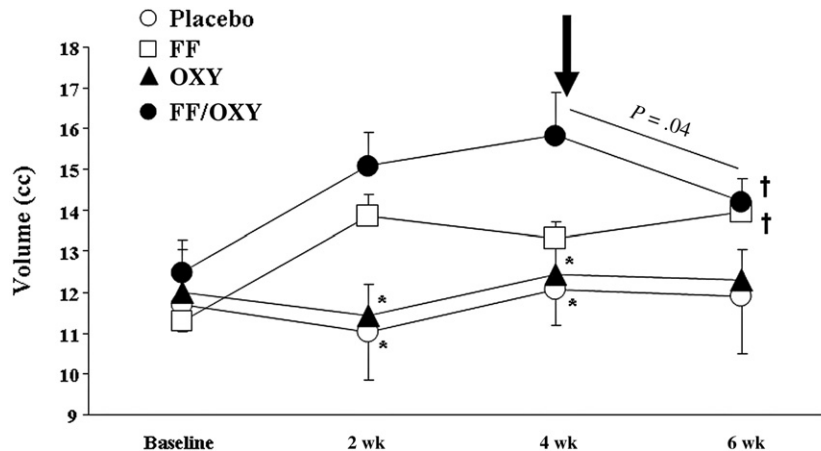


FIG 4. Nasal volume as measured by acoustic rhinometry in mL. The x-axis represents the timeline with baseline measurement and measurements at 2 weeks and 4 weeks of active treatment as well as at 6 weeks after initiation of the study. Treatment was stopped after the 4-week time point as denoted by the solid arrow. * $P \leq .03$ versus FF/OXY. † $P < .04$ versus baseline.

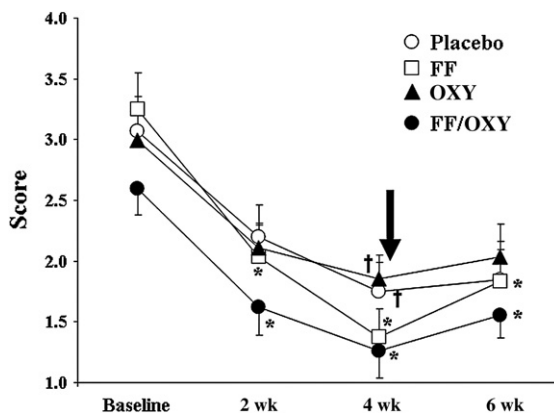


FIG 5. Overall domain of the RQLQ. The x-axis represents the timeline with baseline measurement and measurements at 2 weeks and 4 weeks of active treatment as well as 6 weeks after initiation of the study. Treatment was stopped after the 4-week time point, as denoted by the solid arrow. * $P < .02$ and † $P \leq .01$ versus baseline.

develop inflammation within the mucosa and epithelial changes.¹⁴

The potential for topical decongestants to cause rhinitis medicamentosa is listed as a side effect in the *Physicians' Desk Reference* and prompts limiting their usage to twice per day for 3 to 5 days. The reports addressing this recommendation are divided. Graf and colleagues,¹⁵⁻²² in a series of articles, showed evidence of rebound and also suggested a role for the preservative benzalkonium chloride. In contrast, several studies have shown lack of rhinitis medicamentosa when oxymetazoline or xylometazoline was used for up to 8 weeks.²³⁻²⁵ Various other studies have documented deleterious effects of oxymetazoline on the nasal mucosa.^{14,26,27} In addition to these observations, the recovery from the rebound nasal congestion associated with rhinitis medicamentosa after cessation of topical decongestants can be hastened by the use of intranasal steroids in human beings and guinea pigs.^{6,28-30} Vaidyanathan et al³¹ showed that healthy subjects could develop rebound congestion, which was primarily mediated by α -adrenoreceptors and was reversed by intranasal fluticasone propionate. Thus, the absence of rebound congestion

in our study was expected because of the once-daily dosing of oxymetazoline, and in the combination group the FF may have acted in addition to prevent rhinitis medicamentosa.

Evaluating for rebound in a population with changing degrees of congestion as occurs in patients with perennial allergic rhinitis is difficult. Also, the arms of the study with effective treatments should favorably influence symptoms and airflow assessments. In this study, we chose to look at the potential for rebound both objectively (acoustic rhinometry and NPIF) and subjectively (symptom scores). We compared data at baseline, end of treatment, and end of the 2-week washout period. If rhinitis medicamentosa developed in the oxymetazoline-only group, we would have expected the outcome measures to be worse after treatment compared with placebo treatment and for them to return to baseline after 2 weeks of no treatment. This potential outcome was not observed. If rhinitis medicamentosa developed in the combination group with FF, one would have expected that, toward the later period of treatment, the combination would have been less, instead of more, effective than FF treatment alone. For establishing the absolute safety of once-daily dosing of oxymetazoline, however, a larger number of subjects need to be studied.

The combination of mometasone furoate once daily plus oxymetazoline at 3 sprays per nostril was shown to have a greater effect on RQLQ than mometasone alone, oxymetazoline alone, and placebo.^{32,33} Similar results were shown for the symptom of congestion.^{32,33} The drugs were reported to be safe and without side effects of rhinitis medicamentosa. Our study reached the same conclusions with a lower dose of oxymetazoline, different timing of administration, a different intranasal steroid, and subjects with perennial allergic rhinitis rather than seasonal allergic rhinitis. The fact that other authors observed a positive effect on quality of life, whereas we did not, probably reflects a difference in the number of subjects studied per arm, approximately 140 versus our 15.

We observed a prolonged effect on symptoms after stopping treatment in both FF groups, compared with the response in the placebo and oxymetazoline-only groups. We suspect this to be related to the positive alterations caused by the prolonged use of intranasal steroids on the nasal mucosa. Intranasal steroids have

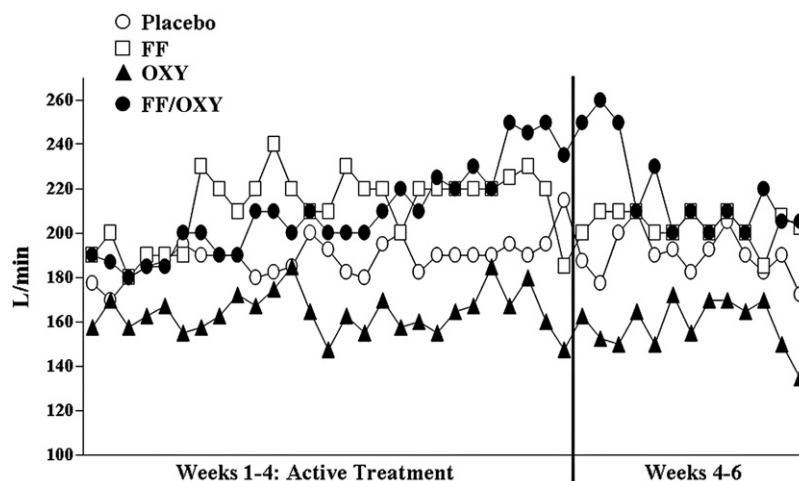


FIG 6. NPIF (sum of AM and PM scores) in liters per minute during the 4 weeks of active treatment and the 2 weeks after cessation of therapy. The solid vertical line represents cessation of therapy. Data are displayed as medians.

been shown to reduce inflammation within the mucosa and to reduce the number of mast cells. The length of time after treatment cessation before these inflammatory processes return to prime the nasal mucosa to antigen exposure is unknown. Interestingly, the additive effect of oxymetazoline and FF did not persist after stopping, suggesting a different mechanism of action.

In sum, we showed that the combination of FF and oxymetazoline has beneficial effects beyond those of FF alone. We believe that the development of such a combination should be pursued by a large multicenter clinical trial, and the current data should not be associated with a change in clinical practice. The combination should increase the number of responders. In addition, the combination does not appear to be associated with rhinitis medicamentosa. On a theoretic basis, the combination might be a useful treatment for patients with nonallergic nasal congestion, with the oxymetazoline treating congestion and the intranasal steroid preventing the development of rhinitis medicamentosa.

Clinical implications: The combination of once-daily FF and oxymetazoline provides efficacy superior to that of FF without causing rhinitis medicamentosa.

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684 Longitudinal Analysis of Regular Use of Cetirizine Demonstrates Consistent Relief from Symptoms of Seasonal Allergic Rhinitis

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RATIONALE: Many adults require regular use of 2nd generation antihistamines to manage the symptoms of seasonal allergic rhinitis (SAR). To evaluate whether cetirizine provides continued symptomatic relief over time, a longitudinal analysis of 6 clinical trials lasting 2 to 4 weeks in duration was performed.

METHODS: Otherwise healthy adults with a history of SAR and experiencing symptoms received cetirizine 5 mg once daily, 10 mg once daily, or 5 mg twice daily in 6 randomized, double-blind, placebo-controlled clinical trials. Subjects scored individual SAR symptoms on a 4-point rating scale. Total symptom severity complex (TSSC) score was the sum of individual SAR symptom scores. Change from baseline in TSSC was analyzed by week and the percent reduction of the group mean from the baseline mean is presented by week.

RESULTS: Efficacy was compared weekly for 156 subjects taking 5 mg cetirizine daily and for 911 subjects taking 10 mg cetirizine daily in 6 trials. Significant symptomatic relief compared to placebo ($p < 0.05$) was demonstrated in each week in all 6 trials. Compared to baseline, cetirizine patients experienced 27.2% to 60.7% improvement in TSSC after 1 week of therapy. The percent reduction in group mean TSSC compared to the baseline mean was maintained each week (32.0% to 68.9%) over a 2- to 4-week treatment period in the 6 trials.

CONCLUSIONS: In adults with a history of SAR, 5- or 10-mg daily doses of cetirizine improved SAR symptoms and maintained a consistent level of relief throughout 2 to 4 weeks of use regardless of dose or dosage regimen.

685 Synergistic Effect of Montelukast and Loratadine on Allergic Rhinitis in Mice

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RATIONALE: To determine the effects of the combination of montelukast and loratadine in a mouse model of allergic rhinitis.

METHODS: Ovalbumin (OVA) sensitized female Balb/c mice were challenged intranasally with OVA without anesthesia on up to 6 consecutive days. Mice received either montelukast (5, 30 mg/kg), loratadine (5, 30 mg/kg), a combination of montelukast (5 mg/kg)/loratadine (5 mg/kg), or vehicle (0.5% methylcellulose) by gavage 1 hr prior to each of the OVA challenges. Respiratory frequency (RF) was monitored by whole body plethysmography at 3 different time points; prior to the first OVA challenge (baseline), just after the 4th OVA challenge (early-phase response (EPR)) and 24 hrs after the 6th OVA challenge (late-phase response (LPR)). Nasal resistance (RNA) was measured in the LPR.

RESULTS: The RF values in sensitized and challenged vehicle-treated mice (positive control) decreased (EPR and LPR) and RNA values were significantly elevated (LPR) compared to baseline values. Single treatment with montelukast (5 mg/kg) or loratadine (5 mg/kg) did not result in any alteration of RF values in the EPR or LPR or RNA in LPR. On the other hand, the combination of both montelukast (5 mg/kg) and loratadine (5 mg/kg) prevented the changes in the EPR and LPR, maintaining RF and RNA values in the normal range.

CONCLUSIONS: Combination treatment with low-dose montelukast and loratadine had therapeutic benefits in preventing both EPR and LPR in a model of allergic rhinitis, even at doses where single therapy proved ineffective.

686 Tolerability of Concomitant Administration of Mometasone Furoate and Oxymetazoline Nasal Sprays Administered Once Daily vs Oxymetazoline Twice Daily, Mometasone Furoate Once Daily, and Placebo in the Treatment of Subjects With Seasonal Allergic Rhinitis

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RATIONALE: Concomitant administration of intranasal corticosteroids and intranasal decongestants may have additive effects in relieving nasal symptoms of allergic rhinitis (AR). This study assessed tolerability of mometasone furoate nasal spray (MFNS) 200 mcg QD and oxymetazoline (OXY) 0.05% given concomitantly, compared with OXY, MFNS, and placebo alone in subjects with seasonal AR (SAR).

METHODS: This phase II, single-blind, placebo-controlled, multicenter trial randomized subjects (aged ≥ 12 years; ≥ 2 -year history of SAR; positive skin-prick test to appropriate seasonal allergen) to 1 of 5 treatment arms: MFNS QD+OXY 1 spray/nostril QD (MFNS+OXY1), MFNS QD+OXY 3 sprays/nostril QD (MFNS+OXY3), MFNS QD, OXY 2 sprays/nostril BID, or placebo for 15 days. Safety evaluations included adverse events (AEs); mean change from baseline in vital signs, electrocardiograms (ECGs), laboratory measurements, and nasal examinations.

RESULTS: Baseline characteristics were similar across all groups (mean age range, 38-40y). Subjects (N=707) were randomized to MFNS+OXY1 (n=146), MFNS+OXY3 (n=139), MFNS QD (n=139), OXY BID (n=141), or placebo (n=142). Study-drug related AEs reported in the respective groups were 13 (9.0%), 11 (7.9%), 5 (3.6%), 9 (6.4%), and 8 (5.6%). Headache was the most frequently reported AE (2.1%, 2.2%, 2.2%, 1.4%, and 0.7%, respectively). There were no study-drug related serious AEs. No clinically relevant changes were observed in laboratory parameters, vital signs, or ECGs in any treatment group. No adverse changes were reported in nasal examinations.

CONCLUSIONS: The combination of MFNS+OXY was well tolerated. The proportion of treatment-emergent AEs was comparable across all treatment groups with no unexpected AEs.

687 Efficacy and Safety of Olopatadine Hydrochloride Nasal Spray, 0.6% in Children 2 to 11 Years of Age with Allergic Rhinitis

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RATIONALE: To evaluate the efficacy and safety of olopatadine hydrochloride nasal spray, 0.6% (Olo), in patients 2 to 11 years of age with allergic rhinitis.

METHODS: Two multi-center, randomized, double-blind, placebo-controlled, parallel-design studies were conducted: Study 1, efficacy and safety in seasonal allergic rhinitis patients 6 to 11 years old, receiving Olo or Vehicle (Veh) 1 or 2 sprays/nostril BID for 2 weeks and Study 2, safety in patients 2 to 5 years old with histories of allergic rhinitis receiving Olo or Veh 1 spray/nostril BID for 2 weeks. Efficacy was assessed in Study 1, based on reflective total nasal symptom scores (rTNSS) and total ocular symptom scores (rTOSS) over the study period. Adverse events and physical examination were assessed in both studies.

RESULTS: In Study 1 (n=1,174), patients treated with Olo experienced superior symptom relief compared to those treated with Veh based on mean rTNSS percent reduction from baseline (1 spray: 24.7% vs. 17.9%, $p=0.0007$; 2 sprays: 26.5% vs. 20.8%, $p=0.012$) and rTOSS (1 spray: 24.5% vs. 6.1%, $p=0.0084$; 2 sprays: 26.3% vs. 8.2%, $p=0.001$). No serious adverse events or clinically relevant differences from baseline in nasal, cardiovascular, or general physical examination parameters were observed in either Study 1 or Study 2 (n=132).

CONCLUSION: Olo 1 spray BID significantly reduced both nasal and ocular symptoms in seasonal allergic rhinitis patients ages 6 to 11. Olo was safe and well tolerated by patients ages 2 to 11 with symptoms of seasonal allergic rhinitis.

681 Comparison Of The Effectiveness And Tolerability Of A Combination Of Nasal Antihistamine+Steroid Sprays With Two Over-The-Counter Nasal Sprays Containing Medicinal Products In Patients Suffering From Seasonal Allergic Rhinoconjunctivitis (SAR): LipoNasal Vs. Nasaleze Vs. Levocabastine + Beclometasone

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RATIONALE: The aim of this study was to investigate the symptom reduction in patients suffering from tree-pollen allergy under treatment with a liposomal nasal spray LipoNasal. Moreover, the tolerability and impact on the patients' quality of life were examined. An investigation of the same parameters was conducted for a cellulosic nasal spray and the control medication levocabastine + beclometasone (combination of antihistamine and glucocorticosteroid).

METHODS: A prospective, controlled, monocenter open-label study was conducted including 60 patients suffering from SAR induced by tree-pollens. Patients were subdivided into 3 treatment groups: LipoNasal; Nasaleze; levocabastine + beclometasone. Effectiveness, tolerability and quality of life were determined by nasal- and conjunctival-symptom-scores, a nasal-spray-sensoric-scale, and the RHINASTHMA-quality-of-life-scale, respectively.

RESULTS: LipoNasal resulted in a significant improvement of nasal ($p=0.003$) and conjunctival ($p=0.005$) symptoms. The nasal symptom relief induced by Nasaleze and levocabastine + beclometasone were also significant. Overall, the tolerability of the 3 nasal sprays can be considered as good and no serious adverse effects were observed. The quality of life of the total population improved significantly during the treatment period. (LipoNasal: $p=0.002$; Nasaleze: $p<0.001$; levocabastine + beclometasone: $p=0.002$). With respect to the 3 treatment groups none showed a significantly higher quality of life ($p=0.750$).

CONCLUSIONS: The treatment of tree-pollen allergy with LipoNasal leads to a significant symptom reduction and a significant improvement of the quality of life. This amelioration does not differ significantly from the therapy according to the guidelines using antihistamine- and glucocorticosteroid-sprays. The tolerability of LipoNasal was evaluated as good.

682 Impact of Concomitant Administration of Mometasone Furoate and Oxymetazoline Nasal Sprays vs Either Drug Alone or Placebo on Quality of Life in Patients with Seasonal Allergic Rhinitis

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RATIONALE: This study assessed impact of concomitant mometasone furoate (MFNS) 200 mcg and oxymetazoline (OXY) 0.5% nasal sprays on quality of life (QoL) in subjects with seasonal allergic rhinitis (SAR).

METHODS: Subjects ≥ 12 y (≥ 2 -y SAR history) were randomized to: MFNS QD + OXY-1 spray/nostril QD (MF+OXY1); MFNS QD + OXY-3 sprays/nostril QD (MF+OXY3); MFNS QD (MFNS); OXY-2 sprays/nostril BID (OXY); placebo in a 15-day, Phase II, single-blind, placebo-controlled, multicenter trial. Baseline to endpoint change in Juniper's Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score was assessed in subjects ≥ 18 y (28 questions/7 domains: activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, emotional problems).

RESULTS: 620 subjects completed the RQLQ (MF+OXY1, $n=129$; MF+OXY3, $n=119$; MFNS, $n=123$; OXY, $n=129$; placebo, $n=120$). MF+OXY combinations demonstrated significant improvements in overall RQLQ score vs placebo at endpoint: least squares mean (LSM) differences: MF+OXY1 (-0.56); MF+OXY3 (-0.83, both $P<0.001$). Corresponding LSM in MFNS group was -0.47 ($P=0.006$). OXY showed no significant improvement in overall RQLQ score vs placebo. MF+OXY3 vs OXY yielded significant improvement in overall RQLQ score (-0.55, $P=0.001$) and 6 domains: activities (-0.65, $P<0.001$), sleep (-0.61,

$P<0.003$), non-nose/eye symptoms (-0.46, $P<0.009$), practical problems (-0.66, $P<0.001$), nasal symptoms (-0.80, $P<0.001$), emotional problems (-0.61, $P<0.001$). MFNS showed significant improvements vs placebo in activities (-0.61, $P=0.001$), practical problems (-0.66, $P=0.001$), sleep (-0.46, $P=0.026$), nasal symptoms (-0.70, $P=0.001$), emotional problems (-0.59, $P=0.001$).

CONCLUSIONS: RQLQ effect size demonstrated clinical benefit of MF+OXY combinations vs placebo and MF+OXY3 vs OXY in subjects with moderate-to-severe SAR. MF+OXY3 group showed greater QoL improvement than MF+OXY1 group.

683 Withdrawn

677 Congestion And Rhinitis Are Common In Fibromyalgia Patients

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RATIONALE: Patients with fibromyalgia experience a large number of different symptoms. We report here the occurrence of upper airway symptoms such as congestion, rhinitis and comorbid conditions in these patients. **METHODS:** We assessed 25 consecutive female patients with fibromyalgia, age median 54 (range 39 to 78) using the 13 questions congestion screener, structured clinical records were used for searching comorbidities such as eczema or asthma, skin prick testing for atopy determination and FeNo, spirometry and impulse oscillometry to determine the existence of a lower airway component of disease.

RESULTS: 20/25 (80%) patients suffered nasal congestion during the previous week, median was 21 (range 6 to 39), 12/25 were skin positive almost all to dust mites, but only 13 fulfill criteria for allergic rhinitis, 8/25 had asthma and 8/25 suffered from eczema.

FeNo values assessed by the Niox Mno trend to be higher in skin test positive patients, respiratory impedance as well was higher in patients with asthma.

CONCLUSIONS: Nasal congestion is very common feature of patients with fibromyalgia and atopic diseases are more frequent in this group than in similar age matched population.

678 The Role of Topical Nasal Steroid in the Treatment of Adenoidal Hypertrophy and Snoring in Pediatric Patients with Allergic Rhinitis

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RATIONALE: Allergic rhinitis (AR) associated with adenoidal hypertrophy (AH) leads to upper airway obstruction and snoring.

We evaluated the effect of fluticasone furoate nasal spray (FFNS) in decreasing adenoidal gland size and snoring in pediatric individuals with AR.

METHODS: Twenty-six pediatric subjects with AH and a history of chronic nasal congestion and snoring received FFNS 27.5 mcg/spray in each nostril once a day for 8 weeks. Group A consisted of 18 subjects (n=18; mean age 6.8 years) with positive skin prick test to environmental allergens. Subjects in Group B (n=8; mean age 7 years), the control group, had a negative skin prick test to environmental allergens. Subjects with hypertrophic tonsils and nasal polyposis were excluded. Efficacy parameters, evaluated at weeks 0 (baseline), 4, and 8, included change in size of the adenoidal gland, assessed by flexible fiberoptic rhinoscopy and graded as percentage according to the degree of obliteration of the choanae, and change in the degree of snoring.

RESULTS: At week 8, mean adenoidal tissue size grade significantly decreased in Group A from 72.3 to 16.3 (-77.5%) during the study period; corresponding decrease for Group B was from 74.1 to 61.5 (-17%). Subjects in Group A experienced a significant amelioration in snoring. Mean average score decreased from 2 at week 0 to 0.5 at week 8 (-75%) compared with Group B mean average score decreased from 1.7 to 1.44 (-18%).

CONCLUSION: FFNS is beneficial in the treatment of AH and in reducing snoring in pediatric patients with AR.

679 Onset and Duration of Action of Concomitant administration of Mometasone Furoate Nasal Spray with Oxymetazoline Nasal Spray Versus Either Drug Alone and placebo in Subjects With Seasonal Allergic Rhinitis

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RATIONALE: Onset and duration of action of concomitant mometasone furoate nasal spray (MFNS) 200 mcg and oxymetazoline (OXY) 0.05% once daily (QD) in seasonal allergic rhinitis (SAR) subjects.

METHODS: Phase 2 study randomized subjects (≥ 12 years, 2-year SAR history) to MFNS QD+OXY 0.05% 1 spray/nostril QD (MFNS+OXY1); MFNS QD+OXY 3 sprays/nostril QD (MFNS+OXY3); MFNS (MFNS/QD); OXY 2 sprays/nostril twice daily (OXY/BID); or placebo (15 days). We report congestion area under curve 0-4 h (AUC[0-4 h]), Day 1 (congestion scores every 15 min for 1 hour post-dosing/every 30 min for 3 hours); change from baseline in AM and PM instantaneous congestion scores (Days 1-15).

RESULTS: Day 1 AUC(0-4)/Congestion were MFNS+OXY1 (2.64/2.72; n=145), MFNS+OXY3 (2.62/2.72; n=138), MFNS/QD (2.59/2.71; n=139), OXY/BID (2.64/2.72; n=140), and placebo (2.64/2.74; n=140, respectively). Day 1 least squares mean (LSM) AUC(0-4) changes were -0.80, -0.92, -0.63, -1.06, and -0.57, respectively. MFNS+OXY1, MFNS+OXY3, and OXY/BID yielded significant improvement vs placebo within 15 min post-dosing through 4 hours ($P \leq 0.041$). MFNS+OXY1, MFNS+OXY3, and MFNS significantly improved both AM and PM instantaneous congestion scores over Days 1-15 compared with placebo ($P \leq 0.002$); there were no significant reductions for OXY/BID vs placebo. For these assessments, both MFNS+OXY combinations yielded superior improvement vs OXY/BID ($P \leq 0.001$), numerical improvement vs MFNS/QD, with MFNS+OXY3 significant vs MFNS in the PM ($P=0.019$). No serious treatment-related adverse events occurred.

CONCLUSIONS: Both MFNS+OXY combinations were well tolerated, relieved congestion significantly faster than MFNS alone (onset of action ≤ 15 min), and provided at least numerically greater relief of morning (pre-dose)/evening congestion than either monotherapy during 2-week treatment.

680 Oxymetazoline (OXY) Hydrochloride Combined with Mometasone Nasal Spray (MNS) for Persistent Nasal Congestion (NC)

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RATIONALE: Nasal glucocorticosteroids (NGCS) are first-line therapy for allergic and non-allergic rhinitis. Data are limited about efficacy and safety of OXY used with NGCS for NC not adequately responding to recommended doses of NGCS.

METHODS: A 20-day randomized DBPC study of subjects > 18 years with a minimum 1-year history of moderate to severe NC which failed to respond to NGCS were stratified to MNS 100 mcg QHS and OXY 0.05% 2 sprays/nostril (s/n) BID vs. MNS 100 mcg QHS + saline placebo (PL) 2 s/n BID. Subjects completed diaries for NC and QOL and underwent intranasal examination for nasal and turbinate changes and rhinorrhea. NGCS were continued following study termination.

RESULTS: 22 subjects met inclusion criteria. The MNS + OXY cohort vs. PL achieved an averaged NC score of 1.68 vs 2.06 (NS), respectively. The treatment group reported 22% improvement in average daily NC score on days 5-7; 14.5% on days 12-14; 13.5% on days 18-20 vs. the MNS + PL of 1.4% worsening on days 5-7; 9.4% improvement on days 12-14; and 6.6% improvement on days 18-20. Slightly more nasal erythema occurred with OXY. No rhinitis medicamentosa (RM) or other side effects occurred in either group.

CONCLUSIONS: MNS + OXY combination for 20 days decreases NC without significant side effects or risk for RM. Larger studies are necessary.